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Contraceptive Technology

Eighteenth Revised Edition

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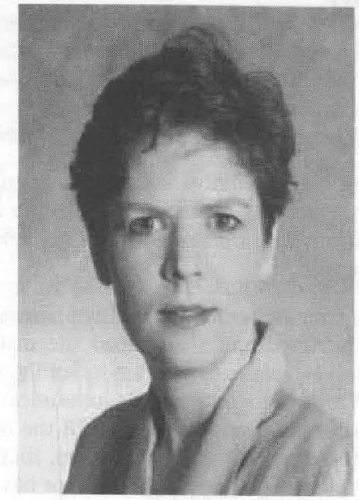

In memory of

Charlotte Ehrengard Ellertson, MPA, PhD

March 2, 1966 – March 21, 2004

Beloved friend, inspiring colleague, visionary scholar, effective activist

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Many individuals contributed to this edition of *Contraceptive Technology*. They helped ensure the completeness, accuracy, timeliness, and usefulness of the information contained herein. The Authors (listed in the first grouping) alone are responsible for errors and opinions.

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* Deceased, March 21, 2004.

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Exhibit 164

1 Expanding Perspectives on Reproductive Health

Deborah Kowal, MA, PA

- Evolving market forces and consumer expectations are changing the scope of reproductive health services.
- Many primary care providers are delivering reproductive health services. Conversely, many reproductive health care providers are delivering primary care services.
- Family planning helps not only individuals and families, but also the community at large.

In recent years, reproductive health care in the United States, in parallel with other medical disciplines, has changed to meet the challenges of evolving market forces and broadened consumer expectations. As a result, integrated reproductive health care has expanded in concept. In many cases, shifting management and insurance schemes have placed reproductive health within the domain of primary care. For an increasing number of women, the clinician who provided only family planning now often serves as their health care provider for all primary care. For others, their primary care provider now delivers the family planning services they may previously have received elsewhere.

A broader scope of family planning services includes not only fertility but also infertility, not only sexually transmitted infections (STIs) but also reproductive tract infections (RTIs) overall, not only menstruation and fertilization but also the preconceptual and interconceptual periods and menopause, and finally, not only reproductive tract problems but the wide range of risk factors that influence a woman's health in general. As reproductive health care expands in scope, however, two goals are paramount. First, the planning, or preventive focus, of family planning must remain a central activity. Second, reproductive health must be recognized for its broader public health impact.

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results have not yet been substantiated by any other studies. Consensus is that it is not prudent to prescribe higher dose pills based on these preliminary data because of the increased risk of thrombosis with high doses of estrogen.[11] Heavier women who used extended cycles of OCs had no increase in pregnancy risk.[12]

Transdermal Patch and Contraceptive Ring

The patch and the vaginal ring have not been in use long enough to permit precise measurements of typical-use failure rates. In comparative trials, the failure rates for patches, vaginal rings, and OCs were low[13,14] and roughly equivalent. Successful utilization rates were statistically higher with the longer acting agents than with the pills that were taken daily. Overall, women who used the patch or vaginal ring were more likely to use their methods correctly and consistently for 13 cycles than were OC users.[15,16] These observations suggest that, in routine practice, the newer long-acting delivery systems may be associated with lower typical-use pregnancy rates than are the pills. However, since this tantalizing possibility has not yet been demonstrated, the authors have decided to quote the same typical failure rates for the pill, the patch, and the vaginal ring (see Chapter 9, The Essentials of Contraception).

One group of potential patch users deserves special counseling. Heavier women, weighing >198 lbs, comprised 3% of the study population but experienced 30% of all the pregnancies in the clinical trial.[17] This decrease in efficacy does not preclude use of the patch by heavier women but does suggest that these women may benefit from additional counseling,[18] including recommending back-up contraception.

Table 19-1 First-year probability of pregnancy* for women using combined hormonal contraceptives compared with other hormonal contraceptives

Method	% of Women Experiencing an Unintended Pregnancy Within the First Year of Use		% of Women Continuing Use at One Year
	Typical Use	Perfect Use	
Combined pill and minipill	8	0.3	68
Evra Patch and Nuva Ring	8**	0.3	68
Depo-Provera	3	0.3	56
IUD			
Paragard (Copper T)	0.8	0.6	78
Mirena (LNG-IUS)	0.1	0.1	81

* See Table 9-2 for pregnancy year failure rates of all methods.
** No data available; assumed to be same as combined oral contraceptives.

Emergency Contraceptive Pills: Treatment initiated within 72 hours after unprotected intercourse reduces the risk of pregnancy by at least 75%. (See Chapter 12 for more information.)

COST

Health department family planning programs in Washington State have paid much less for OCs than for other hormonal contraceptives. In 2001, they reported paying $1.35 per cycle of combined pills, just over one third of the cost of Depo-Provera. In Washington, the discounted cost of OCs to health departments is about 1/20th of the price charged to a private pharmacy chain.[19] The cost of the pills to women paying full price at pharmacies varies somewhat but is becoming higher all the time, ranging from $15 to $50 or even higher per cycle. Generic brands are typically less expensive. Usually, pills cost from $30 to $35 per cycle, one ring costs $40, and a pack of 3 patches (one cycle) costs $42. This means women paying full price pay $390 to $455 per year out of pocket for OCs, just over $500 for the ring and about $550 for the patch. Women whose contraceptives are covered by insurance have to pay a co-pay each month. Purchase of OCs from the Internet, when 3 cycles are bought at a time, can reduce the price to under $20 per cycle with delivery charges extra. Some women travel to Mexico to purchase pills over-the-counter for as little as $3 to $5 per cycle.

ORAL CONTRACEPTIVES

OCs are safe and effective for the vast majority of reproductive-aged women. They are the most extensively studied medications in the history of medicine. Over 80% of U.S. women born after 1945 have used the pill at some time.[1] In the United States, OCs are available only by prescription; in some other countries, they are available over the counter. The keys to successful and safe OC use are selection of appropriate OC candidates, patient motivation, and effective counseling.

Oral Contraceptive Formulations

OCs are available in either monophasic or multiphasic packaging:

- **Monophasic formulations.** Each active pill contains the same doses of the estrogen and progestin.
- **Multiphasic formulations.** The amounts of hormones in the active pills can vary throughout the cycle.
  - Biphasic pills have 2 different combinations of estrogen and progestin in the pills.
  - Triphasic formulations have 3 different combinations. Sometimes the progestin content increases in stepwise progression during the cycle, but some other formulations may also alter the amounts of estrogen given during the cycle. One formulation (Estrostep) holds the progestin dose constant and increases the estrogen content in tablets late in the cycle.

Most pill packs contain 21 active (hormone containing) pills with or without 7 placebo pills (21-pill packs versus 28-pill packs). However, one

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Exhibit 164
JA-0003285

brand (Mircette) includes 21 active pills, 2 placebo pills and 5 pills with 10 mcg EE each. Another preparation (Seasonale) has 84 active pills followed by 7 placebo pills, which reduces the number of withdrawal bleeds to 4 episodes a year. Under development are preparations containing 24 active pills and 4 placebo pills per pack.

ADVANTAGES AND INDICATIONS

Many women harbor profound misinformation about the safety and utility of OCs. A 2000 survey revealed that 41% of those interviewed believed the pill was associated with significant health hazards.[20] However, OCs have numerous attractive features:

General Advantages

1. **Effectiveness.** When taken correctly and consistently, OCs are very effective contraceptives that give women control over their own fertility.
2. **Safety.** Through prudent selection of users (see below), OCs are safer for a woman's health than are pregnancy and delivery. Recent large-scale studies show that OC use does not increase the risk of death among non-smokers.[21]
3. **An option throughout the reproductive years.** Healthy women can safely use OCs throughout their reproductive lives. Age itself is not a reason to avoid OCs. The noncontraceptive benefits of the pill meet the varying needs of women of all ages. Young women may benefit from reduction in severe dysmenorrhea and acne, while at the other end reproductive life, perimenopausal women may benefit from cycle control and hot flash reduction provided by OCs.
4. **Rapid reversibility.** On average, women who stop taking OCs have only a 2-week delay in return of ovulation. Some women (<3%) have a slower return to fertility—the so-called "post-pill amenorrhea"—that is diagnosed 6 months after stopping the pills. Women need to understand that OC use neither hastens nor delays the onset of menopause.

Contraceptive health benefits

1. **Reduction of maternal deaths.** The CDC calculated that there were 11.8 pregnancy-related deaths per 100,000 live births in the last decade of the 20th century, but that there was significant under-reporting.[22] Embolism, hemorrhage, and pregnancy-induced hypertension were the 3 leading causes of death. Considering that nearly half the pregnancies in this country are unintended, prevention of those pregnancies could significantly decrease maternal deaths.

2. **Reduction of ectopic pregnancies.** OCs reduce the risk of ectopic pregnancy by over 90%.[23–25] At least one in 80 pregnancies in the United States is an ectopic pregnancy, the leading cause of maternal death in the first trimester. The CDC reports that 25 women died of ectopic pregnancy in 1992.

Menstrually-related health benefits

1. **Decreased dysmenorrhea.** OCs significantly decrease menstrual cramps and pain. Although the original studies used high-dose formulations, even low-dose formulations help when given in the conventional cyclic fashion.[26] OC use reduces the incidence of all degrees of dysmenorrhea by 60%.[27] Severe dysmenorrhea was reduced by almost 90%.[28] In a randomized clinical trial, low-dose OC users reported fewer absences from school and work and used less pain relief medicine than placebo users. More significant relief of symptoms can be achieved by continuous or extended use, which eliminates withdrawal periods for prolonged periods of time.
2. **Decreased menstrual blood loss.** OCs decrease the number of days of bleeding and the amount of blood women lose each cycle. In women with menorrhagia, high-dose OC use reduced blood loss by 53%.[29] In more recent studies with low dose OCs (30 mcg EE), menstrual blood loss and duration of flow were also decreased.[30] Overall, a 38% to 49% reduction in menstrual blood loss was seen in another study with a 30 mcg EE preparation.[31,32] In addition, nearly 50% of women experience a reduction in duration of menstrual bleeding with OC use.[33] Decreased menstrual blood loss reduces a woman's risk for iron deficiency anemia. If women use any of the extended cycle options, the number of withdrawal bleeds decreases, enhancing these benefits even more.
3. **Reduction in menstrually-related PMS symptoms.** OCs can reduce menstrually-related PMS symptoms such as mastalgia, bloating, cramping, and pain. Drospirenone-containing pills have also been shown to improve symptoms of water retention, negative affect, and increased appetite associated with menses.[34,35]
4. **Decreased anovulatory bleeding.** Low-dose OC use was associated with a more than 80% improvement in dysfunctional uterine bleeding in a randomized, double blind, placebo-controlled study.[36]
5. **Mittelschmerz relief.** By preventing ovulation, OCs can eliminate the midcycle pain some women experience with ovarian follicle swelling and oocyte extrusion.

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Exhibit 164
JA-0003286

6. **Fewer ovarian cyst problems.** Because OCs suppress ovulation, they reduce the risk of hemorrhagic corpora luteal cysts, a condition which can require surgery. Because OCs decrease stimulation of the ovaries by FSH and LH, the incidence of other functional ovarian cysts among women using high-dose OCs was also reduced. Low-dose and multiphasic formulations may help reduce postovulatory cysts;[37,38] however, they do not protect against follicular cyst formation.[39,40]

7. **Improvement in menstrual migraines.** Menstrual migraines are caused by estrogen withdrawal. Cyclic OC use may worsen the intensity of a woman's migraine during her menses; on the other hand, menstrual migraine symptoms may be prevented if she takes active pills every day continuously. (See the section on Headaches, in Managing Side Effects.)

General health benefits

1. **Endometrial and ovarian cancer risk reductions.** When compared with women who have never used OCs, OC users are 40% less likely to develop epithelial ovarian cancer.[41] Ten years or more of use of all monophasic formulations reduces a woman's risk of developing such cancers by 80%.[42] This protection lasts for up to two decades beyond the time the woman takes her last OC.[42,43] Studies that focus on the newer lower dose formulations (<35 mcg EE) have found similar protection levels[43] even in women genetically at higher risk for developing ovarian cancer (BRCA1 mutation cancers).[43,44] Formulations with high doses of progestins protected more than twice as well as OCs with a lower dose of progestins.[45] Women with a family history of ovarian cancer enjoy a greater benefit of ovarian cancer risk reduction than women with no family history.[46] Women with first-degree relatives with ovarian cancer who use OCs for 4 years had a 90% reduction in ovarian cancer risk.[47] One study found that increased duration of OC use did not reduce further the risk of ovarian cancer in BRCA1 or BRCA2 mutation carriers and cautioned against routine use of OCs for chemoprevention.[48] On the other hand, current information has led some to suggest that OCs should be offered to women at high risk for ovarian cancer even if contraceptive benefit is not required.[49]

   OC use for at least 12 months reduces a woman's risk of developing endometrial cancer by about 40%.[50] That risk reduction is increased to 80% in women who use OCs for at least a decade.[41] This protection also endures for up to 20 years after OC discontinuation.[51]

2. **Decreased risk of benign breast conditions.** OC users are less likely to develop fibrocystic breast changes, cysts, or fibroadenoma and are less likely to experience progression of those breast

COLOR PHOTOS
of Combined and Progestin-Only Oral Contraceptives

The eight color pages of pills are organized as follows:

Color photos of pills from lowest to highest estrogen dose

- Progestin-only pills with **no estrogen**: Micronor, NOR-QD, and Ovrette
- Lowest estrogen pills with **20 micrograms** of the estrogen, ethinyl estradiol: Alesse, Levlite, LoEstrin 1/20, and Mircette
- All of the **30- and 35-microgram** pills (all ethinyl estradiol)
- All of the **phasic** pills
- Highest estrogen pills, with **50 micrograms** of estrogen (ethinyl estradiol OR mestranol). Mestranol is converted in the body to ethinyl estradiol; 50 mcg of mestranol is equivalent to 35 mcg of ethinyl estradiol

** There are prominent horizontal or vertical parallel lines ("equal signs") between pills which are pharmacologically exactly the same. The color and packaging of pills dispensed in clinics may differ from pills in pharmacies.*

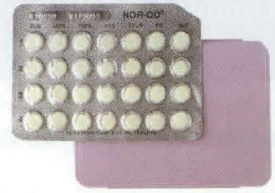
Pills you can prescribe as emergency contraceptive pills

00803745

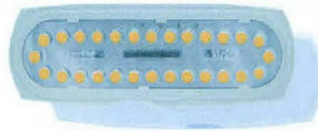
PROGESTIN - ONLY PILLS

MICRONOR® TABLETS 28-DAY REGIMEN
(0.35 mg norethindrone) (lime green)
Ortho-McNeil

=



NOR-QD® TABLETS
(0.35 mg norethindrone) (yellow)
Watson



OVRETTE® TABLETS
(0.075 mg norgestrel) (yellow)
Wyeth

COMBINED PILLS - 20 microgram PILLS

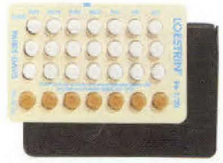
ALESSE - 28 TABLETS
(0.1 mg levonorgestrel/20 mcg ethinyl estradiol)
(active pills pink)
Wyeth

=

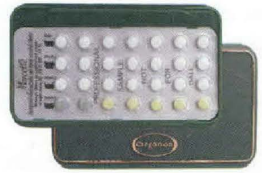
LEVLITE™ - 28 TABLETS
(0.1 mg levonorgestrel/20 mcg ethinyl estradiol)
(active pills pink)
Berlex

=

AVIANE
(0.1 mg levonorgestrel/ 20 mcg ethinyl estradiol)
(active pills orange)
Barr Laboratories



LOESTRIN® FE 1/20
(1 mg norethindrone acetate/20 mcg ethinyl estradiol/75 mg ferrous fumarate [7d])
(active pills white)
Pfizer



MIRCETTE - 28 TABLETS
(0.15 mg desogestrel/ 20 mcg ethinyl estradiol X 21 (white)/ placebo X 2 (green)/10 mcg ethinyl estradiol X 5 (yellow)
Organon

COMBINED PILLS - 30 microgram PILLS

LEVLEN® 28 TABLETS
(0.15 mg levonorgestrel/30 mcg ethinyl estradiol)
(active pills light orange)
Berlex

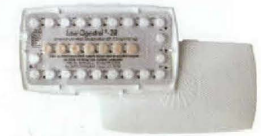
=

LO/OVRAL®-28 TABLETS
(0.3 mg norgestrel/30 mcg ethinyl estradiol)
(active pills white)
Wyeth

||

NORDETTE®-28 TABLETS
(0.15 mg levonorgestrel/30 mcg ethinyl estradiol)
(active pills light orange)
Monarch

||

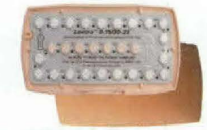


LOW-OGESTREL - 28
(0.3 mg norgestrel/30 mcg ethinyl estradiol)
(active pills white)
Watson

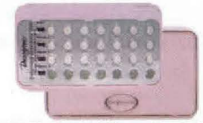
||

SEASONALE
(0.15 mg levonorgestrel/30 mcg ethinyl estradiol)
84 active pills followed by 7 placebo pills
Barr Laboratories

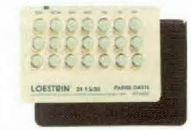
=



LEVORA TABLETS
(0.15 mg levonorgestrel/30 mcg ethinyl estradiol)
(active pills white)
Watson



DESOGEN® 28 TABLETS
(0.15 mg desogestrel/30 mcg ethinyl estradiol)
(active pills white)
Organon



LOESTRIN® 21 1.5/30
(1.5 mg norethindrone acetate/ 30 mcg ethinyl estradiol)
(active pills green)
Pfizer

||

ORTHO-CEPT® TABLETS 28-DAY REGIMEN
(0.15 mg desogestrel/30 mcg ethinyl estradiol)
(active pills orange)

YASMIN 28 TABLETS
(3.0 mg drospirenone/30 mcg ethinyl estradiol)
(active pills yellow)
Berlex

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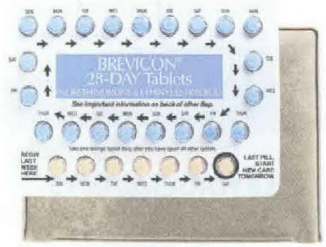
COMBINED PILLS - 35 microgram PILLS

OVCON® 35 28-DAY
(0.4 mg norethindrone/35 mcg ethinyl estradiol)
(active pills peach)
Warner-Chilcott
Now there is a chewable Ovcon-35 pill!

ORTHO-CYCLEN® 28 TABLETS
(0.25 mg norgestimate/35 mcg ethinyl estradiol)
(active pills blue)
Ortho-McNeil



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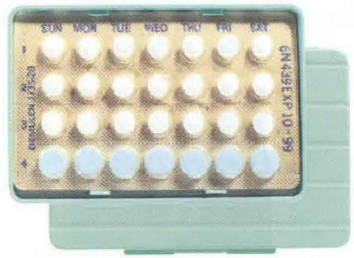
BREVICON® 28-DAY TABLETS
(0.5 mg norethindrone/35 mcg ethinyl estradiol)
(active pills blue)
Watson

MODICON® TABLETS 28-DAY REGIMEN
(0.5 mg norethindrone/35 mcg ethinyl estradiol)
(active pills white)
Ortho-McNeil



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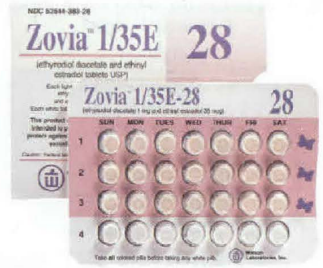


DEMULEN® 1/35-28
(1 mg ethynodiol diacetate/35 mcg ethinyl estradiol)
(active pills white)
Pharmacia

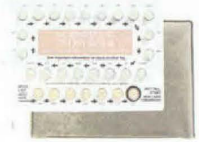
ZOVIA® 1/35E-28
(1 mg ethynodiol diacetate/35 mcg ethinyl estradiol)
(active pills light pink)
Watson

COMBINED PILLS - 35 microgram PILLS (continued)

=

NORETHIN 1/35E-28
(1 mg norethindrone/35 mcg ethinyl estradiol)
(active pills white)
Shire

ORTHO-NOVUM® 1/35 28 TABLETS
(1 mg norethindrone/35 mcg ethinyl estradiol)
(active pills peach)
Ortho-McNeil



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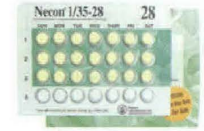
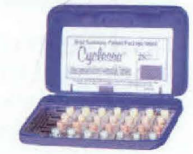


NORINYL® 1+35 28-DAY TABLETS
(1 mg norethindrone/35 mcg ethinyl estradiol)
(active pills yellow-green)
Watson

NECON 1/35-28
(1 mg norethindrone/35 mcg ethinyl estradiol)
(active pills dark yellow)
Watson

COMBINED PILLS - PHASIC PILLS

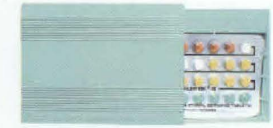
ORTHO TRI-CYCLEN® LO - 28 TABLETS
(norgestimate/ethinyl estradiol)
0.18 mg/25 mcg (7d) (white),
0.215 mg/25 mcg (7d) (light blue),
0.25 mg/25 mcg (7d) (dark blue)
remaining 7 placebo pills are green
Ortho-McNeil



CYCLESSA
(desogestrel/ethinyl estradiol–triphasic regimen)
0.1 mg/25 mcg (7d) (light yellow)
0.125 mg/25 mcg (7d) (orange)
0.150 mg/25 mcg (7d) (red)
Organon

=

=



TRIVORA®
(levonorgestrel/ethinyl estradiol–triphasic regimen)
0.050 mg/30 mcg (6d), 0.075 mg/40 mcg (5d),
0.125 mg/30 mcg (10d) (pink)
Watson

TRIPHASIL®-28 TABLETS
(levonorgestrel/ethinyl estradiol–triphasic regimen)
0.050 mg/30 mcg (6d) (brown),
0.075 mg/40 mcg (5d) (white),
0.125 mg/30 mcg (10d)
(light yellow)
Wyeth

TRI-LEVLEN® 28 TABLETS
(levonorgestrel/ethinyl estradiol–triphasic regimen)
0.050 mg/30 mcg (6d) (brown),
0.075 mg/40 mcg (5d) (white),
0.125 mg/30 mcg (10d)
(light yellow)
Berlex

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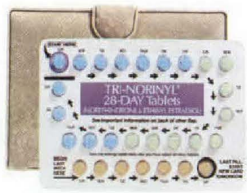
COMBINED PILLS - PHASIC PILLS (continued)

ORTHO-NOVUM® 10/11
28 TABLETS
(norethindrone/ethinyl estradiol)
0.5 mg/35 mcg (10d) (white),
1 mg/35 mcg (11d) (peach)
Ortho-McNeil

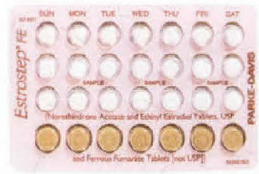
JENEST 28 TABLETS
(norethindrone/ethinyl estradiol)
0.5 mg/35 mcg (7d) (white),
1 mg/35 mcg (14d) (peach)
Organon



TRI-NORINYL®
28-DAY TABLETS
(norethindrone/ethinyl estradiol)
0.5 mg/35 mcg (7d) (blue),
1 mg/35 mcg (9d) (yellow-green),
0.5 mg/35 mcg (5d) (blue)
Watson

ORTHO-NOVUM® 7/7/7
28 TABLETS
(norethindrone/ethinyl estradiol)
0.5 mg/35 mcg (7d) (white),
0.75 mg/35 mcg (7d) (light peach),
1 mg/35 mcg (7d) (peach)
Ortho-McNeil

ORTHO TRI-CYCLEN®
28 TABLETS
(norgestimate/ethinyl estradiol)
0.18 mg/35 mcg (7d) (white),
0.215 mg/35 mcg (7d) (light blue),
0.25 mg/35 mcg (7d) (blue)
Ortho-McNeil

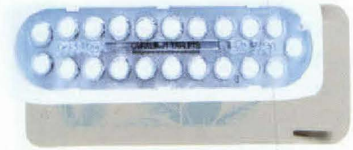


ESTROSTEP® FE
28 TABLETS
(norethindrone acetate/ethinyl estradiol)
1 mg/20 mcg (5d) (white triangular),
1 mg/30 mcg (7d) (white square),
1 mg/35 mcg (9d), 75 mg ferrous fumarate (7d) (white round)
Pfizer

COMBINED PILLS - 50 microgram PILLS

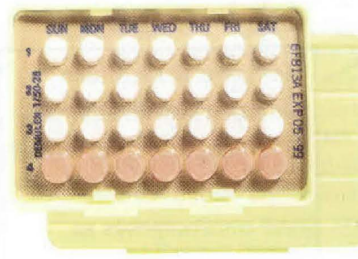
Pills with 50 micrograms of mestranol are not as strong as pills with 50 micrograms of ethinyl estradiol

ORTHO-NOVUM® 1/50
28 TABLETS
(1 mg norethindrone/50 mcg mestranol)
(active pills yellow)
Ortho-McNeil

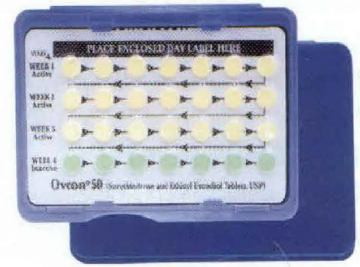


OVRAL - 21 TABLETS
(0.5 mg norgestrel/50 mcg ethinyl estradiol)
(active pills white)
Wyeth

= **OGESTREL**
Watson



DEMULEN® 1/50-28
(1 mg ethynodiol diacetate/50 mcg ethinyl estradiol)
(active pills white)
Pharmacia
A Division of Pfizer



OVCON® 50 28-DAY
(1 mg norethindrone/50 mcg ethinyl estradiol)
(active pills yellow)
Warner-Chilcott

00803748

PILLS AS EMERGENCY CONTRACEPTIVES:

2 Different Approaches: Progestin-Only Pills OR Combined Pills

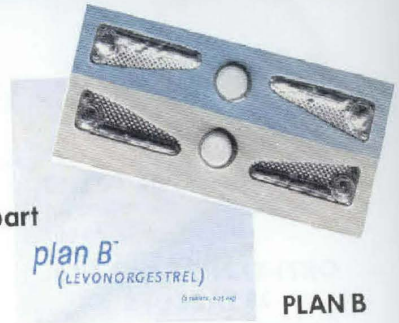
PROGESTIN-ONLY PILLS

Plan B

1 + 1 pill 12 hours apart OR
2 Plan B pills ASAP
after unprotected sex

20 + 20 pills 12 hours apart
Ovrette *(yellow pills)*

(Plan B and Ovrette are NOT carried in all pharmacies. Check in advance. Ask your pharmacy to carry Plan B



PLAN B

Antinausea meds not necessary ←

COMBINED ORAL CONTRACEPTIVES

2 + 2 pills 12 hours apart
Preven* *(blue pills)* OR
Ogestrel *(white pills)*
Ovral *(white pills)*

(Preven Ogestrel and Ovral are NOT carried in all pharmacies. Check in advance.)*

PREVEN*

4 + 4 pills 12 hours apart
Low-Ogestrel *(white pills)*
Lo-Ovral *(white pills)*,
Levora *(white pills)* OR
Levlen *(light orange pills)* OR
Nordette *(light orange pills)* OR
Triphasil *(yellow pills)*,
Tri-Levlen *(yellow pills)* OR
Trivora *(pink pills)*

5 + 5 pills 12 hours apart
Alesse *(pink pills)* OR
Levlite *(pink pills)* OR
Aviane *(orange pills)*

Have your patient take antinausea medication an hour before the first dose if using any of the combined oral contraceptives as emergency contraception. This is not necessary if using Plan B.

* NOTE: Preven Discontinued in 2004

conditions.[52] In one case-controlled study with over 500 women, the risk of benign breast conditions was lower in the OC users, and significantly less in women who started OC use before their first full-term pregnancy.[53] Women who have hyperplasia with atypia are a notable exception; OC use does not confer any protection to these women.[54]

3. **Improvement of androgen sensitivity or androgen-excess conditions** (e.g., polycystic ovary syndrome). In prospective, randomized, placebo-controlled, double-blind trials, women who use OCs have been shown to have a reduction in the numbers and size of acne lesions.[55,56] Dutch surveys reported that OC use reduced the prevalence of acne by over two-thirds.[57] Only 2 formulations have received FDA approval for treatment of mild to moderate acne (OrthoTri-Cyclen and Estrostep), but other formulations with little or no androgenicity and relatively high estrogenicity increase sex hormone binding globulin (SHBG), which is understood to be the main mechanism for OC use in acne treatment. Women with excessive facial or body hair (hirsutism) have reduction in the hair shaft diameter with OC use.[58,59]

4. **Reduced risk of hospitalization for gonorrheal PID.** The risk of cervical gonorrhea infection spreading into the uterus (endometritis), fallopian tubes (salpingitis) or other pelvic organs (PID) is reduced. In studies conducted in the 1980s, when fewer women with PID were treated on an outpatient basis, the risk of hospitalization for PID was reduced by 50% to 60% in current users after 12 months of use.[61] The exact mechanism of this protection is not known. It may be due to thickened cervical mucus blocking sperm penetration, atrophy of the endometrium (fewer days of bleeding), and/or reduction of movement of pathogens into the tube. Similar reductions are not seen in the risk of chlamydial PID.[60]

5. **Suppression of endometriosis.** Current or recent OC use is associated with a lower incidence of symptomatic endometriosis, especially among parous women (see Chapter 6, Menstrual Problems and Common Gynecologic Concerns).[62] The risk of endometrioma was found to be significantly reduced in current OC users over age 25.[63] OCs reduce menstrual flow and presumably decrease retrograde menses, which is generally believed to contribute to endometriosis. Women who have endometriosis can be treated with extended or continuous use of strong progestogenic OCs to induce pseudo-decidualization of the endometriotic implants and to reduce symptoms during use.[64] Such treatment is not curative, however; the implants undergo atrophy during treatment but remain ready for reactivation when OCs are stopped.[65]

6. **Decrease risk of iron deficiency anemia.** By reducing menstrual blood loss, women increase their hemoglobin and ferritin

00803749
Exhibit 164
JA-0003291

levels.[66] This benefit is especially important for women with sickle cell anemia or Von Willebrand's disease, women using anticoagulants or anticonvulsants, and women with fibroids or other causes of primary or secondary menorrhagia (see Chapter 6, Menstrual Problems and Common Gynecologic Concerns).

7. **Treatment of hot flashes and other hormonal fluctuation symptoms** in perimenopausal women.[67,68] (See Chapter 5 on Menopause for more discussion.)

Other potential health benefits

1. **Reduced risk of developing rheumatoid arthritis** (RA). Although early studies suggested that OC use was associated with a reduced risk of RA, there is still controversy about this benefit. One meta-analysis suggested that instead of protecting against the condition, OC use slowed progression of RA,[69] and a later metaanalysis found no protective effect.[70]
2. **Reduced risk of uterine fibroids**. OC users have fewer fibroids, especially with long-term use,[71] but use early in life may increase risk.[72] OCs may control menorrhagia due to uterine myoma. In fact, in many settings, women with moderate-sized fibroids must fail to respond to medical management for menorrhagia (usually with OCs) before they can be considered for surgery.
3. **Reduced risk of fractures**. The impact OC use has on the risk for fracture is still under question. Studies have shown a lower risk for postmenopausal hip fractures,[73] increased bone mineral density (BMD) especially in the lumbar spine,[74] and a slight reduction in osteoporosis.[75] However, one prospective study reported an increased risk of osteoporosis.[76] A comprehensive review of 13 studies of low-dose OCs use found 9 studies showed favorable impact on BMD, and 4 were neutral.[77] If there is a benefit, it may only be in at-risk women with low estrogen levels. OC use increases BMD in young women with hypothalamic amenorrhea.[78] OC use in women with osteopenia due to anorexia nervosa is not sufficient to protect bone, but when added to anabolic agents such as insulin growth factor (IGF), OC use significantly improves that agent's effectiveness.[79] OC use modulates the negative impact of smoking in young women and improves BMD in young women with irregular menses.[80]
4. **Favorable impact on lipids**. EE increases HDL cholesterol and reduces LDL cholesterol. Progestins diminish the magnitude of this favorable impact; the more androgenic formulations have a more pronounced negative effect. Although triglyceride levels increase somewhat with estrogen-containing contraception, there is little concern because those remnants are not atherogenic. However, estrogen-containing contraceptives should be avoided if their use will be anticipated to raise triglyceride levels to 500 mg/dl and place the woman at risk for pancreatitis.
5. **Improved lung mechanics.**[81]
6. **Possible reduced risk for colorectal cancer.**[82]
7. **Influence on sexual enjoyment.** OC use may increase sexual pleasuring, either by increasing libido (less concern about pregnancy) or increasing lubrication. On the other hand, some OC users report decreased libido and more vaginal dryness.
8. **Fewer episodes of seizures, porphyria, and asthma**. These conditions may worsen during a woman's menses. Continuous use of OCs can prevent these problems for months at a time.
9. **Vitamin fortification.** Iron has been added to some placebo pills at the end of the cycle. Work is underway to add 400 mcg of folic acid to both active and placebo pills. Iron deficiency is associated with anemia, and maternal folic acid deficiency contributes to neural tube defects in offspring.

INDICATIONS

Considering the wide range of benefits OCs offer, their use can be particularly attractive for women who desire reversible contraception and have hormone-related problems. It should be noted that OCs might be beneficial in treatment of some of the following conditions (after underlying pathology has been ruled out), even if the woman is not at risk for pregnancy:

- Heavy, painful, irregular menstrual bleeding, or menorrhagia (dysmenorrhea, oligomenorrhea)
- Dysfunctional uterine bleeding
- Recurrent luteal phase ovarian cysts
- Family history of ovarian cancer
- Personal risk for endometrial cancer
- Acne or hirsutism
- Polycystic ovary syndrome (PCOS)

In addition, extended use OC may be particularly helpful for women with

- Premenstrual symptoms (PMS)
- Endometriosis
- Mentally challenged women whose monthly menstruations terrify them and provide a hygiene challenge to their caregivers.
- Anemia due to menorrhagia
- Dysmenorrhea

00803750

Finally, OCs with levonorgestrel or norgestrel may be used for emergency contraception. New studies suggest that OCs with norethindrone may be used for emergency contraception if the more effective formulations are not available (see Chapter 12 on Emergency Contraception).[83]

DISADVANTAGES AND HEALTH COMPLICATIONS

Inform women that OC use may be associated with some disadvantages, many of which can be overcome or managed. Consult the section on Managing Side Effects. Some disadvantages are also discussed in the section on Special Issues.

General Disadvantages

1. **Daily administration.** Inconsistent or incorrect use of OCs reduces protection from the risk of pregnancy and increases the incidence of side effects, such as breakthrough bleeding.
2. **Expense and access.** In many states, insurance plans are not required to cover contraception, so women must pay for their OCs. Often, women are required to return to pharmacies each month to purchase another package. The mismatch between calendar months with 30 to 31 days and pill packs with only 28 pills can present challenges in use.
3. **Need for storage and ready access.** Adolescent women or women whose partners do not want them to use contraception may not have a place to hide their pills. Practitioners need to confirm that the patient's plans for storage are realistic (school lockers are not an answer) and guide them to more private contraceptive methods, if needed. Homeless women and women who travel extensively may have difficulty storing their pill packs.
4. **No protection against STIs.** Women at risk for STIs may use OCs, but they should be advised to reduce their risk for infection by confining their activity to mutually monogamous, uninfected partners, or by using condoms with every act of coitus.

Health Complications

1. **Myocardial infarction (MI).** A pivotal U.S. study showed that low-dose OCs (<50mcg EE) do not significantly increase the risk of MI or stroke in healthy, non-smoking women.[84] Compared to never-users, current users as a group had a relative risk of 1.3 for MI; most of the increased risk was seen in women with known risk factors. A second study supported those findings.[85] Recent metaanalysis of the literature demonstrated that overall current use of OCs increased the risk of MI by 2.48 times. Pills with 20 mcg EE did not increase the risk of MI.[86] Large increases, by

factors of 7 to more than 100, have been observed in the relative risk (RR) of MI and ischemic stroke among OC users who also smoke or have hypertension.[87] The attributable risk of death from cardiovascular disease from low-dose OC use is 0.06 per 100,000 nonsmokers age 15 to 34 and 3.0 per 100,000 nonsmokers aged 35 to 44. However, the risk of death attributable to OC use by low-risk women of any age is less than their risk of mortality from pregnancy.[88]

In an interesting analysis of those data, it was observed that nearly 75% of cases of MI could be attributed to smoking.[89] The third-generation OCs showed no increase in the risk of MIs, but the second-generation formulations apparently doubled the risk.[86] The increase in heart attacks seen with use of combined hormonal contraceptives is due to arterial thrombosis caused by estrogen. This is why women with underlying atherosclerotic coronary vessel damage from smoking, hypertension, and hyperlipidemia are more vulnerable. The effect is reversible. After women stop taking the pill, their risks for MI return to baseline. Once women over age 40 have stopped smoking for 3 to 12 months, they may be candidates for OC use if they have no other contraindications. Women with risk factors for MI may still be candidates for progestin-only methods.

2. **Stroke in high-risk women.** In 2002, a World Health Organization (WHO) panel found no significant increased risk of ischemic or hemorrhagic stroke among nonsmoking women with no history of migraine headaches who use low-dose (<35 mcg EE) OCs,[90] as did a subsequent study.[91] However, OC users who smoke or are hypertensive have a three-fold risk of hemorrhagic stroke compared to those who do not have those risk factors. WHO studies found a significant increase in the risk of ischemic stroke, but not hemorrhagic stroke, among OC users who experienced migraine with aura (odds ratio 3.0, CI 1.3–11.3) and a nonsignificant increase in OC users who reported migraine without aura (OR 3.0, CI 0.7–148) (see Headache section in Managing Side Effects, below).[92] The WHO panel stated that migraineurs with aura have a higher risk of stroke than those without aura, but no study had sufficient proof to examine risk of stroke by type of migraine.[93] There is no difference between second- and third-generation formulations.[94] OC patient package inserts state that the relative risk of hemorrhagic stroke associated with OC use is reported to be 1.2 for non-smokers, 7.6 for smokers, and 25.7 for severe hypertensives. The risk is also greater in older women.[95]
3. **Venous thromboembolism** (VTE). VTE can develop in different organ systems and present with different symptoms as listed on Table 19-2. The rate of thrombosis is 4 to 5 for every 100,000 reproductive-age women, 12 to 20 for low-dose OC users, and 48

00803751

Table 19-2 Circulatory diseases attributable to pills

Diagnosis	Location of Pathology	Symptoms
Thrombophlebitis	Lower leg	Calf pains, swelling, heat or tenderness
Thrombophlebitis	Thigh	Pain, heat, or redness
Pulmonary embolism	Lung	Cough, including coughing up blood, chest pain; shortness of breath
Myocardial infarction	Heart	Chest pain, left arm and shoulder pain, shortness of breath, weakness
Thrombotic stroke	Brain	Headache, weakness or numbness, visual problem, sudden intellectual impairment
Hemorrhagic stroke, including subarachnoid hemorrhage	Brain	Headache, weakness or numbness, visual problem, sudden intellectual impairment
Retinal vein thrombosis	Eye	Headache, complete or partial loss of vision
Mesenteric vein thrombosis	Intestines	Abdominal pain, vomiting, weakness
Pelvic vein thrombosis	Pelvis	Lower abdominal pain, cramps

Source: Stewart F, et al. (1987).

to 60 for pregnant women.[96,97] Pills with 35 mcg EE are associated with a lower risk of VTE than are 50 mg formulations.[98–100] The risk for VTE is highest in the first 1 to 2 years of OC use and then decreases over time. The effects are reversible. Past use of OCs is not associated with increased risk. Smoking does not add to the risk.

Estrogen increases liver production of a variety of clot promoting factors (such as factor VII, factor VIII, factor X and fibrinogen), decreases the production of clot lysing factors (such as antithrombin III and protein S), and increases platelet activity. Progestins alone have no impact on the clotting system, but when combined with estrogen they generally temper estrogen's actions or maintain neutrality. In the mid 1990s, international studies indicated that pills containing the progestins desogestrel and gestodene (not available in the United States) may be associated with higher rates of thrombosis than the formulations containing levonorgestrel and norgestrel.[98–100] U.S. labeling reflects these findings. Since then, it has been shown that there were confounding factors such as duration of use, selection bias (healthy user effect), and detection biases that may have influenced those study outcomes. Norgestimate was not included in the early international studies but was implicated in a subsequent transnational study.[101] Because the new compound, drospirenone, has antiandrogenic effects, it may also allow fuller expression of estrogen's thrombotic impact.[102,103]

In most healthy women, estrogen and progestin together have no clinically significant impact on the coagulation system. Risk factors that place a woman at increased risk for venous thrombosis include obesity, previous venous compromise, and immobilization. However, the increase in VTE risk seen with OC use is most frequently due to inherited disorders such as factor V Leiden mutation or Protein S and C synthesis disorders. The factor V Leiden mutation explains 30% of all deep venous thromboses. In the United States, it is estimated that 5.3% of Caucasians, 2.2% of Hispanics, 1.2% of Blacks and Native Americans, and 0.5% of Asians carry Leiden mutations. Caucasians have a common genetic mutation in prothrombin, which affects 0.7% to 4% of that population.[104] Heterozygous factor V Leiden mutation carriers have thrombotic risk 6 to 8 times higher (24 to 40/100,000), and homozygous carriers have risk about 10 times greater than in the general population. When a carrier uses OCs, her VTE risk rises to 120 to 150/100,000 a year.[105] (For further discussion, see section on Patient Selection.)

4. **Hypertension.** OCs increase circulating levels of angiotensin II. Some women are very sensitive to angiotensin II levels, which can increase both their diastolic and systolic blood pressure readings. Both estrogen and progestin enhance aldosterone activity, which results in fluid retention, which, in turn, also contributes to an increase in blood pressure. The vast majority of women who use OCs will have no significant increase in either diastolic or systolic blood pressure measurements, although a 3 to 5 mm rise is not uncommon. However, 1% to 3% of women who use modern, low-dose OCs will, over time, experience increases in their blood pressure readings, which, if attributable to OC use, will normalize within 3 months of stopping estrogen-containing contraceptives. The women whose readings do not return to normal should undergo a standard work-up, although most will be found to have essential hypertension. Some women may need to begin antihypertensive agents as well as discontinuing OCs.

5. **Glucose tolerance and diabetes.** OCs currently available in the United States do not adversely affect carbohydrate metabolism.[106] Older OC formulations with high doses of sex steroids had a more profound impact on glucose tolerance and in some instances resulted in hyperglycemia with hyperinsulinemia. In the CARDIA study, current use of OCs was associated with lower glucose levels and perhaps with a lower odds ratio of diabetes.[107] Concerns have been raised about OC use in women at risk for developing diabetes because progesterone is a competitive inhibitor of the insulin

00803752

Exhibit 164

JA-0003294

receptor and estrogen influences the release of insulin from the pancreatic islet cells and decreases insulin sensitivity.[108] High-risk women, such as those with a history of gestational diabetes who used OCs with low progestin content (Ovcon-35), had no higher risk of developing glucose intolerance or overt diabetes than the controls who used non-hormonal methods when both groups were studied for up to 7 years.[109]

6. **Gallbladder disease.** Recent studies of low-dose OCs do not show the increased risk of cholelithiasis and cholecystitis associated earlier with high-dose OCs. However, it may still be possible that low-dose OCs accelerate the development of symptomatic gallbladder disease in women with preexisting stones or sludge. OCs do not increase the risk of gallbladder cancer.[110]

7. **Cholestatic jaundice.** The active transport of bile can be impaired by high-dose combined hormonal contraceptives, resulting in cholestatic jaundice with pruritus. This condition reverses with discontinuation of hormones. The incidence in the general population using low-dose formulations is not known but is assumed to be very rare.

8. **Hepatic neoplasms.** Benign liver tumors have been associated with the use of high-dose OCs, especially long-term use. Focal nodular hyperplasia may be increased nearly 3-fold in OC users.[111] Adenomas are the most significant, since they can cause rupture of the liver capsule, extensive intraperitoneal hemorrhage, and even death. Women may or may not have abdominal pain with adenomas; their liver function tests are usually normal. Palpate the liver edge as part of the annual physical exam. If the liver is enlarged or tender, discontinue hormonal contraception and evaluate with MRI or CT tests; ultrasound is not reliable. Tumor regression is expected after stopping OCs.

   Hepatocellular carcinoma risk is not increased with OC use.[112] Use of hormonal contraception by high-risk women (with chronic hepatitis B virus) did not appear to increase the risk of hepatitis cellular carcinoma beyond their baseline elevated risk.

9. **Chlamydia/HIV.** Women who use OCs are at increased risk for acquiring chlamydia cervicitis.[113,114] In a study of Kenyan professional sex workers, users of OCs had an increased risk (hazard ratio 1.8, C1.1–2.9) of becoming infected with chlamydia when compared with women using no contraceptives.[115]

   OCs influence transcription of natural antimicrobials in the human endometrium, which might increase a woman's vulnerability to upper-tract chlamydia or HIV infection.[116] Although a recent study shows that OCs thicken the vaginal epithelium,[117] hormonal contraception might increase a woman's vulnerability to HIV infection by reducing its barrier protection, by increasing the number or permissiveness of susceptible cells, or by directly affecting viral expression.[118] Clearly, all women at risk for STIs should limit their sexual activity to one uninfected, monogamous partner or, at a minimum, use latex or polyurethane condoms with every sexual act.

10. **Melanoma.** A pooled analysis of 10 case-controlled studies involving nearly 2,400 cases of melanoma revealed no correlation between OC use and the development of melanoma. No effect of duration of use or current use was observed.[119] However, it is recommended that women with a history of melanoma refrain from getting pregnant or using hormonal contraception for at least 3 years after their original therapy, since the risk of recurrence is highest at this time.

11. **Leiomyoma** (uterine fibroids) contain both estrogen and progesterone receptors. Since fibroids often shrink after menopause, when estrogen levels decrease, it has been suggested that estrogen-containing contraceptives might increase the growth of these benign uterine tumors. However, clinical studies with low-dose OCs have found no impact on the risk of developing new fibroids or increasing the size of pre-existing fibroids.[120–122] In fact, OCs are often used to control excessive menstrual bleeding caused by fibroids.

12. **Cervical dysplasia and cervical carcinoma.** OC users have a statistically significant higher risk of developing cervical dysplasia compared to women who use no method of contraception or who rely on tubal ligation. Cervical dysplasia and cervical carcinoma are caused by the human papillomavirus (HPV), especially HPV 16 and 18. OC users may have more unprotected intercourse with multiple partners. However, combined hormonal methods cause eversion of the cervical os, which not only increases metaplasia in nulliparous women but exposes those vulnerable metaplastic cells to HPV. OC use may be associated with artifacts that mimic ASC-US (glycogen vacuoles create perinuclear halos in OC users) on liquid-based cytology tests. Reflex HPV testing will demonstrate that two-thirds of those women have no virus.[123]

    OC users do not need to have cervical cytology testing more frequently than required by their other risk factors. Similarly, they do not need to be tested with more sensitive cytologic modalities because they use OCs.

    Women who use OCs for more than 5 years and who are infected with HPV have a 3- to 4-fold increased risk for in situ and invasive

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squamous cell cervical carcinoma.[124] However, a similarly large increase in the risk of cervical cancer was seen in another study in women with HPV infection who had 7 or more pregnancies (RR 8.29). Pregnancy before 18 years of age increases the relative risk (RR) for cervical cancer to 10.71.[125] A large meta-analysis of 28 studies including 12,531 women with cervical cancer found a 1.1 relative risk after 5 years of OC use, RR 1.6 after 5 to 10 years, and RR 2.2 more than 10 years.[126] Studies demonstrate that OC use may increase the risk of adenocarcinoma (cancer of the "glandular" cells of the cervix).[127]

13. **Breast cancer.** A recent study shows that among women aged 35 to 64 years, current or former use of OCs is not associated with an increased risk for developing breast cancer.[128] An older meta-analysis of 90% of the women's literature found that current users had a 25% increased risk of being diagnosed with breast cancer, although all the excess risk disappeared 10 years after stopping the pills. The cancers diagnosed in those studies were more localized.[129] The remaining question is the effect OCs may have on the development of breast cancer in women under age 35, when the disease is very rare. (See Most Frequently Asked Questions, below).

14. **Special issues for drospirenone-containing OCs.** Drospirenone has antimineralocorticoid activity, which introduces the potential for hyperkalemia in high-risk patients; the 3 mg of drospirenone found in Yasmin has the same impact on electrolytes as a 25 mg dose of spironolactone. Women receiving daily, long-term treatment for chronic conditions or diseases with medications that may increase serum potassium should have their serum potassium levels checked during the first treatment cycle. Drugs that may increase serum potassium include ACE inhibitors, angiotensin-II receptor antagonists, potassium-sparing diuretics, heparin, aldosterone antagonists, and NSAIDS. Note that *intermittent* use of NSAIDS does not pose any problems.

PATIENT SELECTION

Patient selection is the key to safe OC use. The benefits of OCs generally far outweigh any significant adverse events. However, some women have medical conditions or personal habits that increase their risk of developing serious complications with use of combined hormonal contraception.

Cigarette smokers over age 40 face a greater mortality risk with ongoing OC use than they would experience with pregnancy and, therefore, should not use OCs or other estrogen-containing contraceptives. Similarly, heavy smokers (>15 cigarettes/day) over age 35 should avoid estrogen-containing methods, according to product labeling. Many clinicians will not provide combined pills for women over the age of 35 if they smoke at all. (See discussion on Smokers in section on Special Populations.)

Combined hormonal contraceptives should not be used by women with an increased propensity to form blood clots, polycythemia vera, or a personal history of thrombosis, stroke or heart attack, advanced diabetes, labile hypertension, estrogen sensitive malignancies (such as breast cancer), active liver problems, and migraines with focal neurologic symptoms. Although the relative risk of thrombosis is greatly increased in women who have factor V Leiden mutations, routine screening for these rare mutations is not recommended prior to prescribing estrogen-containing contraceptives. However, it may be very appropriate to test (not screen) women who have a strong family history of multiple, unexplained clots in many family members, especially at a young age. Table 19-3 lists conditions from pill package labeling that are listed as contraindications.

PRECAUTIONS

To guide family planning programs, WHO has developed a more comprehensive list of precautions in providing combined hormonal contraceptives, which are summarized in Table 19-4.[130] Use of hormonal contraception by women who have medical conditions are ranked into four different categories. Category 4 conditions preclude the use of combined hormonal contraceptives. Conditions in Category 3 may be adversely impacted by combined hormonal contraceptives, and the risks generally outweigh the benefits. Providers should exercise caution if these agents are used and carefully monitor these OC users for adverse effects. The WHO recognized in its Category 2 that some conditions may trigger potential concerns with hormonal contraceptives, but the benefits of contraceptive use with these conditions usually outweigh the risks. Category 1 conditions raise no concerns about OC use, and OC use should not be restricted.

PROVIDING ORAL CONTRACEPTIVES

Explore the patient's medical and reproductive health history and her family history to ensure that she has no reason to avoid using combined hormonal contraception (see Tables 19-3 and 19-4 on WHO Medical Eligibility Criteria). Discuss the potential noncontraceptive benefits and examine all her lifestyle issues to ensure that she has a secure plan for where to keep her pill pack and can realistically expect to take a pill a day. Anticipatory counseling about safety concerns can reduce later discontinuation. Determine if she wants to have monthly withdrawal bleeding

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or if she would prefer less frequent bleeding episodes. Ask if she has any other complaints that need to be addressed at this visit. In particular, find out if she needs any STI testing or if she needs emergency contraception now or may need it in the future. Advise her to follow safer sex practices.

Measure the woman's blood pressure. It may be prudent to do a breast examination, but a pelvic examination is *not* needed for an asymptomatic woman prior to initiating OCs,[131,132] even if the woman has not had a recent Pap smear. STI screening, if needed, can be urine-based. No other screening tests are routinely needed unless her history or blood pressure indicate a need for further assessment.[133]

Table 19-3 Medical conditions precluding OC use, as listed in pill package inserts (PPI)

There are specific medical conditions that indicate a woman should not use OCs. The FDA-approved pill package inserts (PPI) list a somewhat different set of medical conditions that preclude OC use than do the WHO medical eligibility criteria. Below is the FDA-approved package insert list of medical conditions that indicate OCs "should not be used." The category assigned in the WHO medical eligibility criteria (Table 19-4) is included in the adjacent column.

Medical Conditions Precluding OC Use (PPI)	WHO Category
• Thrombophlebitis or thromboembolic disorder	4
• Past history of deep vein thrombosis or thromboembolic disorders	4
• Cerebrovascular or coronary artery disease	4
• Valvular heart disease with thrombogenic complications	4
• Uncontrolled hypertension	4
• Diabetes with vascular involvement	3/4
• Headaches with focal aura	4
• Major surgery with prolonged immobilization	4
• Breast cancer	4
• Carcinoma of the endometrium	1
• Other known or suspected estrogen-dependent neoplasia	Not discussed
• Undiagnosed abnormal genital bleeding	2
• Cholestatic jaundice of pregnancy	2
— Jaundice with prior pill use	3
• Acute or chronic hepatocellular disease with abnormal liver function, hepatic adenomas, or hepatic carcinomas	4
• Known or suspected pregnancy	"Not applicable"
• Hypersensitivity to any component of the product	Not discussed

Table 19-4 WHO Medical eligibility criteria for low-dose combined oral contraceptives (COCs), patches and rings, 2004

LOW-DOSE COMBINED ORAL CONTRACEPTIVES (COCs) <35 mcg of ethinylestradiol	COCs do not protect against STI/HIV. If there is risk of STI/HIV (including during pregnancy or postpartum), the correct and consistent use of condoms is recommended, either alone or with another contraceptive method. Male latex condoms are proven to reduce the risk of STI/HIV.
CONDITION	CATEGORY I = Initiation C = Continuation
PERSONAL CHARACTERISTICS AND REPRODUCTIVE HISTORY	
PREGNANCY	NA
AGE	
a) Menarche to <40 years	1
b) ≥ 40 years	2
PARITY	
a) Nulliparous	1
b) Parous	1
BREASTFEEDING	
a) < 6 weeks postpartum	4
b) ≥ 6 weeks to <6 months postpartum (primarily breastfeeding)	3
c) ≥ 6 months postpartum	2
POSTPARTUM (in non-breastfeeding women)	
a) <21 days	3
b) ≥ 21 days	1
POST-ABORTION	
a) First trimester	1*
b) Second trimester	1
c) Immediate post-septic abortion	1
PAST ECTOPIC PREGNANCY	1
HISTORY OF PELVIC SURGERY (including Caesarean section)	1
SMOKING	
a) Age <35 years	2*
b) Age ≥ 35 years	
(i) < 15 cigarettes/day	3*
(ii) ≥ 15 cigarettes/day	4*

(continued)

* For more detailed clarifications, consult the WHO website.

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Table 19-4 WHO Medical eligibility criteria for low-dose combined oral contraceptives (COCs), patches and rings, 2004—*(cont'd)*

CONDITION	CATEGORY I = Initiation C = Continuation
OBESITY	
≥ 30 kg/m^2 body mass index (BMI)	2
CARDIOVASCULAR DISEASE	
MULTIPLE RISK FACTORS FOR ARTERIAL CARDIOVASCULAR DISEASE (such as older age, smoking, diabetes and hypertension)	3/4*
HYPERTENSION	
a) History of hypertension, where blood pressure CANNOT be evaluated (including hypertension during pregnancy)	3*
b) Adequately controlled hypertension, where blood pressure CAN be evaluated	3*
c) Elevated blood pressure levels (properly taken measurements)	
(i) systolic 140–159 or diastolic 90–99	3
(ii) systolic ≥160 or diastolic ≥100	4
d) Vascular disease	4
HISTORY OF HIGH BLOOD PRESSURE DURING PREGNANCY (where current blood pressure is measurable and normal)	2
DEEP VENOUS THROMBOSIS (DVT)/ PULMONARY EMBOLISM (PE)	
a) History of DVT/PE	4
b) Current DVT/PE	4
c) Family history of DVT/PE (first-degree relatives)	2
d) Major surgery	
(i) with prolonged immobilization	4
(ii) without prolonged immobilization	2
e) Minor surgery without immobilization	1
KNOWN THROMBOGENIC MUTATIONS (e.g., Factor V Leiden, prothrombin, protein S, protein C, and antithrombin deficiency)	4*

(continued)

* For more detailed clarifications, consult the WHO website.

Table 19-4 WHO Medical eligibility criteria for low-dose combined oral contraceptives (COCs), patches and rings, 2004—*(cont'd)*

CONDITION	CATEGORY I = Initiation C = Continuation
SUPERFICIAL VENOUS THROMBOSIS	
a) Varicose veins	1
b) Superficial thrombophlebitis	2
CURRENT AND HISTORY OF ISCHAEMIC HEART DISEASE	4
STROKE (history of cerebrovascular accident)	4
KNOWN HYPERLIPIDAEMIAS (screening is *not* necessary for safe use of contraceptive)	2/3*
VALVULAR HEART DISEASE	
a) Uncomplicated	2
b) Complicated (pulmonary hypertension, atrial fibrillation, history of subacute bacterial endocarditis)	4

NEUROLOGIC CONDITIONS	I	C
HEADACHES		
a) Non migrainous (mild or severe)	1*	2*
b) Migraine		
(i) without aura		
Age < 35	2*	3*
Age ≥ 35	3*	4*
(ii) with aura (at any age)	4*	4*
EPILEPSY	1*	
DEPRESSIVE DISORDERS	1*	

(continued)

* For more detailed clarifications, consult the WHO website.

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Table 19-4 WHO Medical eligibility criteria for low-dose combined oral contraceptives (COCs), patches and rings, 2004—*(cont'd)*

CONDITION	CATEGORY I = Initiation C = Continuation
REPRODUCTIVE TRACT INFECTIONS AND DISORDERS	
VAGINAL BLEEDING PATTERNS	
a) Irregular pattern *without* heavy bleeding	1
b) Heavy or prolonged bleeding (includes regular and irregular patterns)	1*
UNEXPLAINED VAGINAL BLEEDING (suspicious for serious condition)	
Before evaluation	2*
ENDOMETRIOSIS	1
BENIGN OVARIAN TUMOURS (including cysts)	1
SEVERE DYSMENORRHOEA	1
TROPHOBLAST DISEASE	
a) Benign gestational trophoblastic disease	1
b) Malignant gestational trophoblastic disease	1
CERVICAL ECTROPION	1
CERVICAL INTRAEPITHELIAL NEOPLASIA (CIN)	2
CERVICAL CANCER (awaiting treatment)	2
BREAST DISEASE	
a) Undiagnosed mass	2*
b) Benign breast disease	1
c) Family history of cancer	1
d) Cancer	
(i) current	4
(ii) past and no evidence of current disease for 5 years	3
ENDOMETRIAL CANCER	1
OVARIAN CANCER	1

(continued)

* For more detailed clarifications, consult the WHO website.

Table 19-4 WHO Medical eligibility criteria for low-dose combined oral contraceptives (COCs), patches and rings, 2004—*(cont'd)*

CONDITION	CATEGORY I = Initiation C = Continuation
UTERINE FIBROIDS	
a) Without distortion of the uterine cavity	1
b) With distortion of the uterine cavity	1
PELVIC INFLAMMATORY DISEASE (PID)	
a) Past PID (assuming no current risk factors for STIs)	
(i) with subsequent pregnancy	1
(ii) without subsequent pregnancy	1
b) PID-current or within the last 3 months	1
STIs	
a) Current purulent cervicitis or chlamydial infection or gonorrhea	1
b) Other STIs (excluding HIV and hepatitis)	1
c) Vaginitis without purulent cervicitis	1
d) Increased risk of STIs (e.g., multiple partners or partner who has multiple partners)	1
HIV/AIDS	
HIGH RISK OF HIV	1
HIV-INFECTED	1
AIDS	1*
OTHER INFECTIONS	
SCHISTOSOMIASIS	
a) Uncomplicated	1
b) Fibrosis of liver	1
TUBERCULOSIS	
a) Non-pelvic	1*
b) Known pelvic	1*
MALARIA	1

(continued)

* For more detailed clarifications, consult the WHO website.

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Table 19-4 WHO Medical eligibility criteria for low-dose combined oral contraceptives (COCs), patches and rings, 2004—*(cont'd)*

CONDITION	CATEGORY I = Initiation C = Continuation
ENDOCRINE CONDITIONS	
DIABETES	
a) History of gestational disease	1
b) Non-vascular disease	
(i) non-insulin dependent	2
(ii) insulin dependent	2
c) Nephropathy/retinopathy/neuropathy	3/4*
d) Other vascular disease or diabetes of >20 years' duration	3/4*
THYROID	
a) Simple goiter	1
b) Hyperthyroid	1
c) Hypothyroid	1
GASTROINTESTINAL CONDITIONS	
GALL-BLADDER DISEASE	
a) Symptomatic	
(i) treated by cholecystectomy	2
(ii) medically treated	3
(iii) current	3
b) Asymptomatic	2
HISTORY OF CHOLESTASIS	
a) Pregnancy-related	2
b) Past COC-related	3
VIRAL HEPATITIS	
a) Active	4
b) Carrier	1
CIRRHOSIS	
a) Mild (compensated)	3
b) Severe (decompensated)	4

(continued)

* For more detailed clarifications, consult the WHO website.

Table 19-4 WHO Medical eligibility criteria for low-dose combined oral contraceptives (COCs), patches and rings, 2004—*(cont'd)*

CONDITION	CATEGORY I = Initiation C = Continuation
LIVER TUMORS	
a) Benign (adenoma)	4
b) Malignant (hepatoma)	4
ANAEMIAS	
THALASSAEMIA	1
SICKLE CELL DISEASE	2
IRON DEFICIENCY ANEMIA	1
DRUG INTERACTIONS	
COMMONLY USED DRUGS WHICH AFFECT LIVER ENZYMES	
a) Certain antibiotics (rifampicin)	3*
b) Certain anticonvulsants (phenytoin, carbamezapine, barbiturates, primidone, topiramate, oxcarbazepine)	3*
OTHER ANTIBIOTICS (excluding rifampicin)	1
a) Griseofulvin	2
b) Other antibiotics	1
ANTIRETROVIRAL THERAPY	2*

* For more detailed clarifications, consult the WHO website.

Source: WHO (2004),[131] with permission.
For references and update, please consult
http://www.who.int/reproductive-health/publications/MEC_3

FOLLOW-UP

Because side effects can appear in the first few months of OC use, a follow-up visit at 3 or 6 months is quite commonly recommended. A woman who has used the pill for 3 to 6 months, has no problems, and wants to continue the pill, may be given 7 to 13 packets (a 6-month to 1-year supply). One author of this chapter strongly recommends providing only 3 cycles of pills at the first visit with a 9-month refill, followed by a 12-month supply every subsequent year. Recent suggestions that it may be appropriate to provide OCs over-the-counter also suggest that new OC users may not need such frequent reassessment.[134,135] An alternative approach is to prescribe or give a woman a full year's supply of pills the very first visit and then encourage a revisit or two in the first year for a blood pressure

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Exhibit 164
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and headache check. After a woman has used OCs for 1 year, you could consider prescribing a full year's supply of pills (or even 18 cycles) in an effort to increase OC continuation rates.

Women who are planning major surgery requiring prolonged immobilization should discontinue use of estrogen-containing OCs 1 month prior to surgery. Similarly, women being treated with anticoagulants should stop their OCs 1 month prior to finishing their anticoagulant.

CHOICES FOR PILL INITIATION

Quick start. For the Quick Start method, the patient takes the *first* pill in the pill pack on the day of her office visit, as long as she is not pregnant and not in need of emergency contraception. If she needs emergency contraception, she should take both tablets of Plan-B or its equivalent at once on the visit day, and start her pills no later than the next day. Tell her to use a back-up method with her pills for at least 7 days. Her next menses will be delayed until she completes the active pills in her pack and starts the placebo pills. If she has concern about an undetectable early pregnancy, she can start her pills and be instructed to return for a urine pregnancy test in 2 to 3 weeks, or do one at home. Alternatively, she can use a first-day start. The hormones in the pills will not adversely affect an early pregnancy and the prompt repeat pregnancy testing will detect the pregnancy early enough to begin the pregnancy care she chooses.

The Quick Start approach was more successful getting women started on the pill than are the two methods discussed below; more women were using the pill in the third cycles, especially if they had menstrually-related problems.[136] However, it is an off-label practice. The reason Quick Start is preferred is because other approaches leave a time gap between the time the patient is prescribed her pills and the time she is intended to start taking them. As many as 25% of young women starting by one of the conventional start methods (see below) failed to begin taking the pills as instructed because they had conceived in the interim, forgot the pill-taking instructions, failed to fill the prescription, or were worried about taking the pill after their visit.[137,138] Quick Start does not increase irregular spotting or bleeding.[139]

First-day start. The first-day start was introduced to gain early control of ovarian follicles during the first cycle. In this approach, a woman takes her first pill on the first day of her next period. It is important to have the woman determine that her period is normal—that it occurs at the predicted time and is preceded by symptoms that are usual for her. If there is any question that the menses is not normal, have her rule out pregnancy before she starts her pills.

Sunday start. The Sunday start was the most common method for starting pills for decades. Women were told to start their first active pill on the first Sunday of their menses. For example, if a woman were to start bleeding on Friday, she should take her first pill two days later on Sunday. If her period were to start on Sunday, she should start on that day. Make sure the patient understands that she should not wait to start the first pill on the Sunday after her menses ends. Today, the Sunday start is not generally recommended because it is often difficult for women to get refills when they need them on weekends. In addition, many women are working outside the home and prefer not to menstruate during their work week. A Sunday start often requires that a back-up method be used for 7 days.

SWITCHING FROM OTHER METHODS

Women who switch from other methods can start OCs immediately, using the guidelines for the pill Quick Start initiation. For example, women who have implants or IUDs removed can start their OCs that same day and be told to use a back-up contraceptive method for the next week. Women who have had recent unprotected intercourse can be given Plan B emergency contraception (EC) immediately and start their OCs no later than the next day coupled with a back-up method for at least 7 days. A urine pregnancy test in 2 to 3 weeks may be offered to detect any EC failures. Women using injectable methods generally start their OCs at the end of the effective period of the injection. However, if a woman is amenorrheic as a result of the injection and is late for reinjection, she can start the OCs the same day with a 7-day course of a back-up method. For any woman with a recent history of unprotected intercourse, provide EC, OCs, and back-up methods followed by a repeat pregnancy test in 2 to 3 weeks.

CHOOSING A PATTERN OF PILL USE

1. **Monthly cycling 21/7.** Conventional pill packaging contains 3 weeks of active pills followed by 7 placebo pills to provide a predictable, coordinated withdrawal bleed that women will interpret to be a normal menses. Pioneers in the development of the birth control pill touted this feature as a distinct benefit for women,[140] which it was at the time.
2. **Shortened pill-free interval.** It is possible that the 7-day pill-free interval allows too much time for follicular development and increases to the failure rate with low-dose OCs. Shortening the pill-free interval with 20 mcg EE pills from 7 to 5 days suppressed ovarian activity more effectively.[141] One way to implement this approach is to have the patient use the "first-day start" for every cycle, in which she begins a new pill pack each month on the first day of her withdrawal bleeding. If she has no menses by the 5th placebo pill day, she should start her new pack that day. A pregnancy test is not necessary, but may provide comfort to the woman. In a trial comparing a 23-day regimen to the traditional 21-day regimen of 20 mcg EE pills, the withdrawal bleeding was shorter in the group using more active pills.[142] Mircette has 21 active pills, 2 placebos, and 5 pills with 10 mcg EE.
3. **Extended use.** Recent studies have found that many of the "pill side effects" (such as headache, cramping, breast tenderness, bloating

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